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EXAMINER	
XIE, XIAOZHEN	

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1646	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/568,806	HARARI, DANIEL	
	Examiner	Art Unit	
	XIAOZHEN XIE	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 May 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-40* is/are pending in the application.

4a) Of the above claim(s) *5,7,15-31 and 33-40* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6,8-14 and 32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 February 2006* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *20080226, 20080926*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *sequence alignment*.

DETAILED ACTION

Status of Application, Amendments, And/Or Claims

The Information Disclosure Statements (IDS) filed 26 February 2008 and 26 September 2008 have been entered. Applicant's preliminary amendment of the claims filed 21 February 2006 has been entered.

Election/Restrictions

Applicant's election of Group I, claims 1-14 and 30, in the response received 7 May 2010 is acknowledged. In the response, Applicant elected SEQ ID NO: 81 as the one splice variant of an ErbB ligand.

Applicant indicates that it is not clear whether the restriction requirement (mailed 11/9/2009) indicates that there is an additional election of a single specie from SEQ ID NOs: 74-84, 93, 95-104 and 109-121, because there is no statement that an election of specie is required. Applicant also indicates that since product claims are elected, rejoinder of the process claims of Groups IV and VI pursuant to MPEP 821.04 is requested once an elected product claim is subsequently found to be allowable.

As set forth in the Office action (mailed 11/9/2009), the polypeptides of Group I, represented by different SEQ ID NOs, are drawn to multiple distinct products which have distinctly different structures. For example, the amino acid sequences shown in the SEQ ID NOs represent splicing variants for different ErbB family ligands, such as EGF, HB-EGF, NGR, etc. Thus, each of the products is drawn to a distinct invention, and the PCT rules do not provide for the examination of multiple products, multiple

methods of making one product, or multiple methods of using one product in one application. Accordingly, the requirement to elect one splicing variant is not a species election, but a distinct invention.

Since product claims are elected, the process claims (Groups IV and VI) that depend from or otherwise include all the limitations of the allowable product claim will be rejoined in accordance with the provisions of MPEP § 821.04 once the elected product claim is subsequently found allowable, withdrawn Process claims that depend from or otherwise include all the limitations of the patentable product will be entered as a matter of right if the amendment is presented prior to final rejection or allowance, whichever is earlier. Amendments submitted after final rejection are governed by 37 CFR 1.116; amendments submitted after allowance are governed by 37 CFR 1.312. In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103, and 112. Until an elected product claim is found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowed product claim will not be rejoined. See "Guidance on Treatment of Product and Process Claims in light of *In re Ochiai, In re Brouwer* and 35 U.S.C. § 103(b)," 1184 O.G. 86 (March 26, 1996). Additionally, in order to retain the right to rejoinder in accordance with the above policy, Applicant is advised that the process claims should

be amended during prosecution either to maintain dependency on the product claims or to otherwise include the limitations of the product claims. Failure to do so may result in a loss of the right to rejoinder. Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

The requirement is still deemed proper and is therefore made FINAL. Claims 1-40 are pending. Claims 5, 7, 15-31 and 33-40 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Claims 1-4, 6, 8-14 and 32 are under examination to the extent they read on SEQ ID NO: 81.

Information Disclosure Statement

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Drawings

The drawings are objected to under 37 CFR 1.83(a) because they fail to show details as described in the specification. For example, Figures 1, 2, 4 and 5B are not legible, in particular, the letters or numbers being highlighted or shaded. Also, the letters in Figure 3 and 6 are fading. Any structural detail that is essential for a proper understanding of the disclosed invention should be shown in the drawing. MPEP § 608.02(d). Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Specification

The disclosure is objected to because of the following informalities:

The specification does not contain as a first paragraph, a claim to benefit of priority to any application. Upon review of the Oath/Application Data Sheet, it would appear that applicant is claiming benefit of priority to a provisional application 60/495,898. The first line of the specification should include updated cross-reference to related applications. See 37 CFR 1.78 and MPEP § 201.11. Correction is required.

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code (for example, on page 64, Table 5, page 69, line 11). Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-14 are rejected under 35 U.S.C. § 101 because the claimed invention is directed to non-statutory subject matter. The claimed protein can be found in nature. Products of nature do not constitute patentable subject matter under 35 U.S.C. § 101. Amending the independent claim to require that the protein is “isolated” would be remedial.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 6, 8-14 and 32 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a polypeptide comprising a splice variant of an ErbB ligand encoded by differential exon usage comprising a truncated ErbB receptor-modulating EGF domain devoid of the C-loop of the EGF domain (claim 1); wherein the splice variant comprising the truncated EGF domain having only the first four of the six conserved cysteines found in an intact EGF domain, and the fourth conserved cysteine of the truncated EGF domain is the penultimate amino acid at the C terminus of the polypeptide (claims 2, 3); wherein the splice variant further comprising an amino acid sequence encoded by an alternative exon other than the second exon encoding conserved cysteines five and six of the intact ErbB receptor-modulating EGF domain (claim 6); wherein the splice variant has at least 90% or 95% homology to the amino acid sequence of a known ErbB ligand between cysteine 1 and 4 (claims 8, 9); wherein the N terminal flanking sequences preceding the cysteine 1 are at least 90% homologous to a known ErbB ligand (claim 10); wherein the splice variant retains binding activity to at least one member of the ErbB/EGF receptor family, and exerts inhibitory activity on at least one member of the ErbB/EGF receptor family (claims 11-14).

The claims are broad in that they encompass a large genus of polypeptides that are not sufficiently describes in the specification. What applicant has described in the specification is the identification of a splicing variant of an ErbB ligand which functions as an antagonist for the ErbB receptor. The specification describes a bioinformatics approach used for identifying these splicing variants (pp. 25). The specification discloses that in analyzing the genomic sequences encoding the mammalian ErbB ligands, specifically, the neuregulin/EGF ligand family, which exon organization at the site of the EGF domain is conserved, it was found that not only the position of the exon-exon junction for Exon A (encoding the first component of the EGF modulating domain of ErbB ligands, including C1-C4) and Exon B (encoding the second component of the EGF modulating domain of ErbB ligands, including C5-C6) is conserved for all mammalian ErbB ligands, in what would typically be considered as "intronic" region just beyond Exon A, an invariant stop codon has been identified and is encoded both in-frame and immediately downstream of Exon A (FIG. 4). The specification discloses that this provides indirect evidence to support that alternative isoforms of all mammalian ligands may exist in which the encoded proteins harbor truncated EGF domains; specifically, such splice variants would encode the EGF domain to one amino acid beyond C-4 (FIG. 4). The specification discloses that similar topology was found for genes encoding ErbB ligands from other vertebrate species, e.g., mouse, bovine and chicken. The specification discloses the amino acid sequences translated from the genomic sequences of 11 members of the neuregulin/EGF ligand family which polypeptides are truncated at one amino acid beyond C-4 (Fig. 4). These amino acid

sequences are set forth in SEQ ID NOs: 73-84 (the elected amino acid sequence of SEQ ID NO: 81 derived from HB-EGF gene). The specification further discloses that the theoretically identified truncated ErbB ligand splicing variants actually exist in nature, for example, there exists a truncated NRG1 variant, which is identical to other typical NRG1 alpha isoforms, except that its sequence ends one amino acid after the fourth cysteine of the EGF domain.

The specification also discloses a search of EST, NR, and patent databases for sequences that encode ErbB ligand variants or potentially encode ErbB ligands, and categorizes the protein sequences into two classes (pp. 29):

Class I: sequences truncated after C-4; in addition to SEQ ID NOs: 73-84 described above, other amino acid sequences include SEQ ID NOs: 85-110 (pp. 30, Table 2); and

Class II: sequences including Exon A but lack Exon B, resulting in the predicted expression of protein of varying lengths extending beyond that of a shortened EGF domain (to the conserved C-4), and the extended portion depending on the alternative exon sequences that are present beyond exon A; the amino acid sequences in this class include SEQ ID NOs: 111-127 (pp. 31-32, Table 3).

Except the splicing variants set forth in the SEQ IDs stated above (i.e., SEQ ID NOs: 73-84 and 85-110 for class I splicing variants, and SEQ ID NOs: 111-127 for class II splicing variants), Applicant does not provide the detailed chemical structure for other ErbB splicing variants encompassed by the claims. Indeed, the sequences represented

by these SEQ IDs are almost all that were available at the time of the present invention, which have the genome organization required for such splicing variants. Also, the specification does not provide sufficient description for homologous sequences of the splicing variants. Obviously, in the absence of more information with regard to the nucleic acid or amino acid sequences, the skilled artisan cannot envision the detailed chemical structure of the encompassed polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991).

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making of the claimed product, or any combination thereof. In this case, there is no sufficient disclosure for complete or partial structure. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (*See Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of peptides, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that is part of the invention and reference to a method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only the splicing variants set forth in SEQ ID NOs: 73-84 and 85-110 (for class I splicing variants) and SEQ ID NOs: 111-127 (for class II splicing variants), but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written

description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claims 1-4, 6, 8-14 and 32 are further rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

An isolated polypeptide comprising a splice variant of an ErbB ligand with the amino acid sequence set forth in SEQ ID NO: 81 (a splicing variant of HB-EGF), wherein the splice variant of an ErbB ligand is encoded by differential exon usage comprising a truncated ErbB receptor-modulating EGF domain which has only the first four of the six conserved cysteines found in an intact EGF domain; and wherein the fourth conserved cysteine of the truncated EGF domain is the penultimate amino acid at the C-terminus of the polypeptide,

does not reasonably provide enablement for the broad genus of polypeptides. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in *In re* Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: the breadth of the claims, the nature of the

invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention based on the content of the disclosure. See also *Ex parte* Forman, 230 USPQ 546 (BPAI 1986).

The claims are broad in that they encompass a large genus of polypeptides, i.e., splicing variants of any ErbB liagnd. The structural requirements for these polypeptides include "comprising a truncated EGF domain devoid of the C-loop of the EGF domain", or "comprising only the first four of the six conserved cysteines found in an intact EGF domain". In addition, these polypeptides may further comprise an amino acid sequence encoded by an alternative exon other than the second exon encoding conserved cysteines five and six of the intact EGF domain; and the splice variants also include those having homology to the amino acid sequence of a known ErbB ligand. Furthermore, these splice variants are required to retains binding and inhibitory activity to at least one member of the ErbB/EGF receptor family.

As set forth above, Applicant has disclosed the identification of a splicing variant of an ErbB ligand which functions as an antagonist for the ErbB receptor. Using a bioinformatics approach (pp. 25), Applicant has identified the splicing variants for the neuregulin/EGF ligand family, which are characterized by differential exon usage, resulting in the encoded proteins harboring a truncated EGF domain; specifically, such splice variants comprise only the first four of the six conserved cysteines found in an intact EGF domain because of a stop codon in the intronic region at the exon-exon

junction between Exon A (encoding the first component of the EGF modulating domain of ErbB ligands, including C1-C4) and Exon B (encoding the second component of the EGF modulating domain of ErbB ligands, including C5-C6). As a result of the stop codon, the polypeptides are truncated in the EGF domain at one amino acid beyond C-4 (FIG. 4). The specification discloses the amino acid sequences translated from the genomic sequences of 11 members of the human or murine neuregulin/EGF ligand family which polypeptides are truncated at one amino acid beyond C-4 (Fig. 4). These amino acid sequences are set forth in SEQ ID NOs: 73-84 (the elected amino acid sequence of SEQ ID NO: 81 derived from HB-EGF gene). The specification further discloses that the theoretically identified truncated ErbB ligand splicing variants actually exist in nature, for example, there exists a truncated NRG1 variant, which is identical to other typical NRG1 alpha isoforms, except that its sequence ends one amino acid after the fourth cysteine of the EGF domain. The specification further discloses a search result of EST, NR, and patent databases for sequences that encode ErbB ligand variants or potentially encode ErbB ligands, and categorizes the protein sequences into class I and II (pp. 29): Class I represents sequences that are truncated after C-4 (in addition to SEQ ID NOs: 73-84 described above, other amino acid sequences include SEQ ID NOs: 85-110) (pp. 30, Table 2); and Class II represents sequences which include Exon A but lack Exon B, resulting in the predicted expression of protein of varying lengths extending beyond that of a shortened EGF domain to the conserved C-4, and the extended portion depending on the alternative exon sequences that are

present beyond exon A (the amino acid sequences in this class include SEQ ID NOs: 111-127) (pp. 31-32, Table 3).

In the Examples, the specification disclose three synthesized class I peptides, human EGF(1-32) (SEQ ID NO: 77), human NGR2(1-32) (SEQ ID NO: 74), and mouse EGF(1-32) (SEQ ID NO: 185) (pp. 66-68). The specification discloses that the synthesized peptides do not potentiate mitogenesis of the BaF/3-EGFR cells (pp. 73); further, in a BIACORE analysis, hNGR-2(1-32) and mEGF(1-32) failed to demonstrate measurable binding to immobilized soluble ErbB1 and ErbB2, but weak binding to Betacellulin was noted, whereas no binding of hEGF(1-32) peptide to the immobilized Betacellulin was detected(pp. 74-75, and Fig. 6).

Despite the disclosure of a number of amino acid sequences (e.g., SEQ ID NOs: 73-84 and 85-110 for class I splicing variants, and SEQ ID NOs: 111-127 for class II splicing variants), Applicant has not provided objective evidence that these splicing variants, most of them are predicted proteins, actually have any activity/function, let along the binding activity and inhibitory activity to at least one member of the ErbB/EGF receptor family. While the prior art teaches one such molecules,such as HGR-γ and SF HB-EGF (see the following 35 U.S.C. 102 section), the prior art, however, does not provide compensatory guidance for making and using the genus of splicing variants or ErbB ligands as broadly claimed. Indeed, the data shown in the specification demonstrates that even for a molecule having the exact structure as recited, it does not necessarily show the required activity/function (see e.g., hEGF(1-32)). Furthermore, many of the disclosed sequences are from EST, these sequences, as acknowledged by

Applicant, are only partial sequences (pp. 29, lines 25-27), and the encoding amino acid sequences for the full-length polypeptides may not be known yet. Thus, without detailed structural information for the genus of molecules, and without further evidence regarding the correlation of structure to function, one of an ordinary skill in the art would not know how to make and use the polypeptides as claimed. The scope of patent protection sought by Applicant as defined by the claims fails to correlate reasonably with the scope of enabling disclosure set forth in the specification.

Due to the large quantity of experimentation necessary to generate a large number of the splicing variant polypeptides recited in the claims, and determine their activity/function and usefulness, the lack of direction/guidance presented in the specification, the absence of working examples, the complex nature of the invention, the state of the prior art which fails to provide compensatory guidance, and the breadth of the claims, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3, 6, 8-14 and 32 are rejected under 35 U.S.C. 102(b) as being anticipated by Eppenberger et al. (WO 99/14323, Int'l. Pub. Date: 25 March 1999).

Eppenberger et al. teach heregulin variants with a truncated EGF domain and pharmaceutical compositions thereof (see Abstract). Eppenberger et al. teach that by screening a cDNA library generated from a HBC cell line, a novel heregulin splicing variant, named HRG-γ, is identified, which is characterized by a truncation in the EGF-like domain. Specifically, a stop codon interrupts the EGF-like motif after the 4th cysteine, and the protein terminates with the penultimate amino acid at the C-terminus (pp. 11, lines 29-29, and Fig. 1). Eppenberger et al. teach that HRG-γ is identical in the amino acid sequence to HRG-α and HRG-β except the truncation (Fig. 1). Eppenberger et al. also made the HRG-γ-EGFP fusion proteins (Fig. 7). Eppenberger et al. teach the biological activities of HRG-γ, which was found to be unable to increase tyrosine phosphorylation or ErbB2 as compared to HRG-β(177-246) peptide (pp. 14, line 35, bridging pp. 15, line 5).

While Eppenberger et al. do not expressly teach that HRG-γ retains the binding activity to at least one member of the ErbB/EGF receptor family, and exerts inhibitory activity on at least one member of the ErbB/EGF receptor family (e.g., when in a 100-fold molar excess or less), this activity would reasonably be considered to be inherent since it has the same structure as recited in the claims. A compound and all of its properties are inseparable (*In re Papesch*, 315 F.2d 381, 137 USPQ 43 (CCPA 1963)), as are their processes and yields (In re Von Schickh, 362 F.2d 821, 150 USPQ 300 (CCPA 1966)).

Therefore, Eppenberger et al. anticipate the instant claims.

Claims 1, 2, 4, 6 and 8-14 are rejected under 35 U.S.C. 102(b) as being anticipated by Loukianov et al. (Gene, 1997, Vol. 195(1):81-86).

Loukianov et al. teach a short form of heparin-binding EGF-like growth factor (SF HB-EGF). Loukianov et al. teach that SF HB-EGF mRNA is a product of alternative splicing. Loukianov et al. teach that like normal HB-EGF, SF HB-EGF contains the signal peptide, the propeptide, the heparin-binding domain and the first two conservative disulfide loops of the EGF unit. Loukianov et al. teach that SF HB-EGF lacks the third disulfide loop, the spacer, the transmembrane and the cytoplasmic domains; instead, SF HB-EGF has a nine amino acid tail (see Abstract). The amino acid sequence of SF HB-EGF is shown in Fig. 1, which comprises the same sequence as SEQ ID NO: 81 of the instant invention (see sequence alignment). The SF HB-EGF protein shown in Fig. 1 comprises a truncated EGF domain having only the first 4 of the 6 cysteines found in an intact EGF domain.

While Loukianov et al. do not expressly teach that SF HB-EGF retains the binding activity to at least one member of the ErbB/EGF receptor family with significantly reduced biological activity compared to an equimolar concentration of at least one known agonist ligand, and exerts inhibitory activity on at least one member of the ErbB/EGF receptor family (e.g., when in a 100-fold molar excess or less), these activities would reasonably be considered to be inherent since it has the same structure as recited in the claims. A compound and all of its properties are inseparable (*In re Papesch*, 315 F.2d 381, 137 USPQ 43 (CCPA 1963)), as are their processes and yields (In re Von Schickh, 362 F.2d 821, 150 USPQ 300 (CCPA 1966)).

Therefore, Loukianov et al. anticipate the instant claims.

Conclusion

NO CLAIM IS ALLOWED.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Xiaozhen Xie, Ph.D whose telephone number is 571-272-5569. The examiner can normally be reached on M-F, 8:30-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary B. Nickol, Ph.D. can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Xiaozhen Xie/
Xiaozhen Xie, Ph.D.
June 11, 2010